TITANIUM DIOXIDE

Risk Assessment Update

2024 GFoRSS Webinar Series

1 October 2024

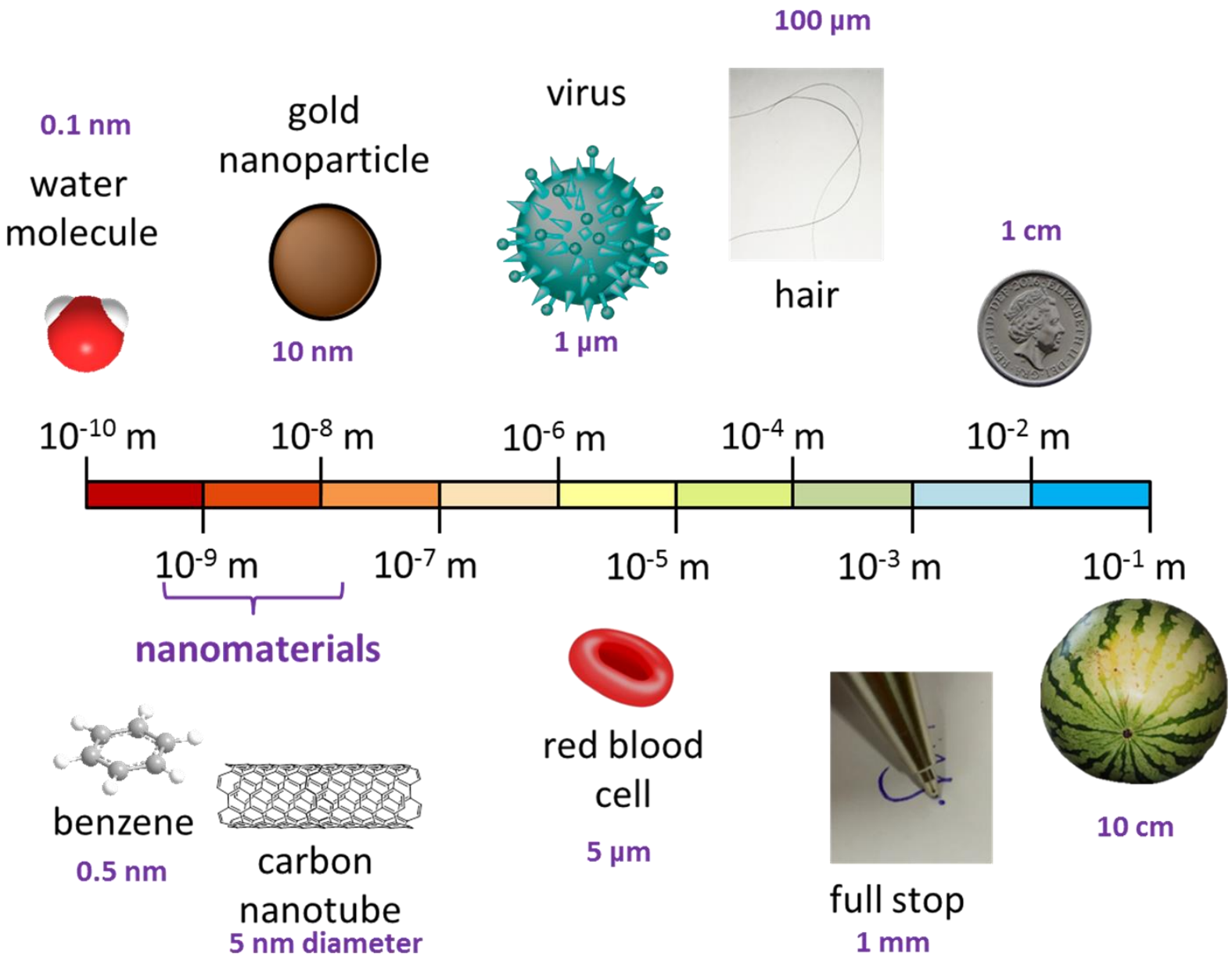
Mr. Mark Feeley, Former Associate Director, Bureau of Chemical Safety, Food Directorate, Health Canada, GFoRSS Senior Food Chemical Safety Expert

Ti Background

- Titanium is the ninth most abundant element on Earth.
- The largest use of titanium is in the form of titanium(IV) oxide (TiO_2).
- TiO_2 is used primarily as a pigment in paint, plastics, enamels, paper, food packaging materials and PCP (toothpaste, cosmetics, sun screens, etc.)
- Also approved for use as a food colouring agent in a broad range of food categories
  - Dairy products, processed meats, cereals, confectionaries, food supplements, etc.
- TiO_2 brightens or whitens food products and also adds texture to foods (anti-caking agent)
- TiO_2 confers a white color and increased opacity with an optimal particle diameter of 200-350 nm.
- TiO_2 particles less than 100 nm are transparent to visible light and are not functional as a pigment.

Safety Assessments

- TiO2 has been approved for use as a food additive since 1966 (US FDA)
- JECFA's original assessment in 1969 concluded TiO2 was insoluble, poorly bioavailable and did not produce systemic toxicity if absorbed.
- An acceptable daily intake (ADI) of "not limited" was assigned (no toxicological concerns)
- Based on the analytical methods available at the time, it was estimated < 5% by mass of food-grade TiO2 was comprised of particles in the nanoscale (< 100 nm)
- More recent analysis has suggested up to 36% of food-grade TiO2 is in the nanoscale.
- EFSA (2021) published an updated safety assessment of TiO2 as a food additive, which included consideration of studies performed with TiO2 nanoparticles.
- EFSA concluded they could not rule out a concern for genotoxicity and consequently could not establish a safe level for daily intake of the additive. Previous ADI and approval for use as a food additive in the EU was withdrawn.


100 µm
virus
gold nanoparticle
0.1 nm
water molecule
hair
1 cm
10 nm
1 µm
10^{-10} m
10^{-8} m
10^{-6} m
10^{-4} m
10^{-2} m
10^{-9} m
10^{-7} m
10^{-5} m
10^{-3} m
10^{-1} m
nanomaterials
red blood cell
5 µm
10 cm
benzene
0.5 nm
carbon nanotube
5 nm diameter
full stop
1 mm

ChemBam

EFSA Reevaluations of TiO2 (E 171)

2016

- Taking into account the presumed limited absorption, TiO2 did not raise any toxicity concerns and its use as a food additive would not be of concern. E 171 not considered to be a nanomaterial.

2019

- Based on new EFSA guidance re. nanotechnology, additional studies were reviewed with TiO2 nanoparticles (NPs) which were considered by EFSA to be relevant to E 171

2021

- TiO2 particles have the potential to induce DNA strand breaks and chromosomal damage, but not gene mutations. A concern for genotoxicity of TiO2 particles that may be present in E 171 could not be ruled out and therefore E 171 can no longer be considered as safe when used as a food additive

2022

- EC removed the authorization to use titanium dioxide (E 171) in foods

2024

- Similar updated reevaluations by HC, FDA*, FSANZ, UK FSA and JECFA have not agreed with the EFSA conclusion

EFSA Reevaluations of TiO2 (E 171)

- Positive results for in vivo MN and CA with TiO2 NPs (5-50 nm), Comet Assay (liver, spleen)
- TiO2 particles have the potential to induce DNA strand breaks and chromosomal damage, but not gene mutations
- An association between TiO2 induced DNA strand breaks/chromosome damage and oxidative stress seen with experimental models using blood, GI tract, liver, lung
- EFSA concluded that a concern for genotoxicity of TiO2 particles that may be present in E 171 cannot be ruled out.
- A cut-off value for TiO2 particle size with respect to genotoxicity could not be identified and there is uncertainty on whether a threshold mode of action existed

JECFA TiO2 (INS 171)

1969

- TiO2 is a very insoluble compound. Studies in several species, including man, show neither significant absorption nor tissue storage following ingestion of titanium dioxide.
- Establishment of an acceptable daily intake for man is considered unnecessary (no toxic effects).

2021

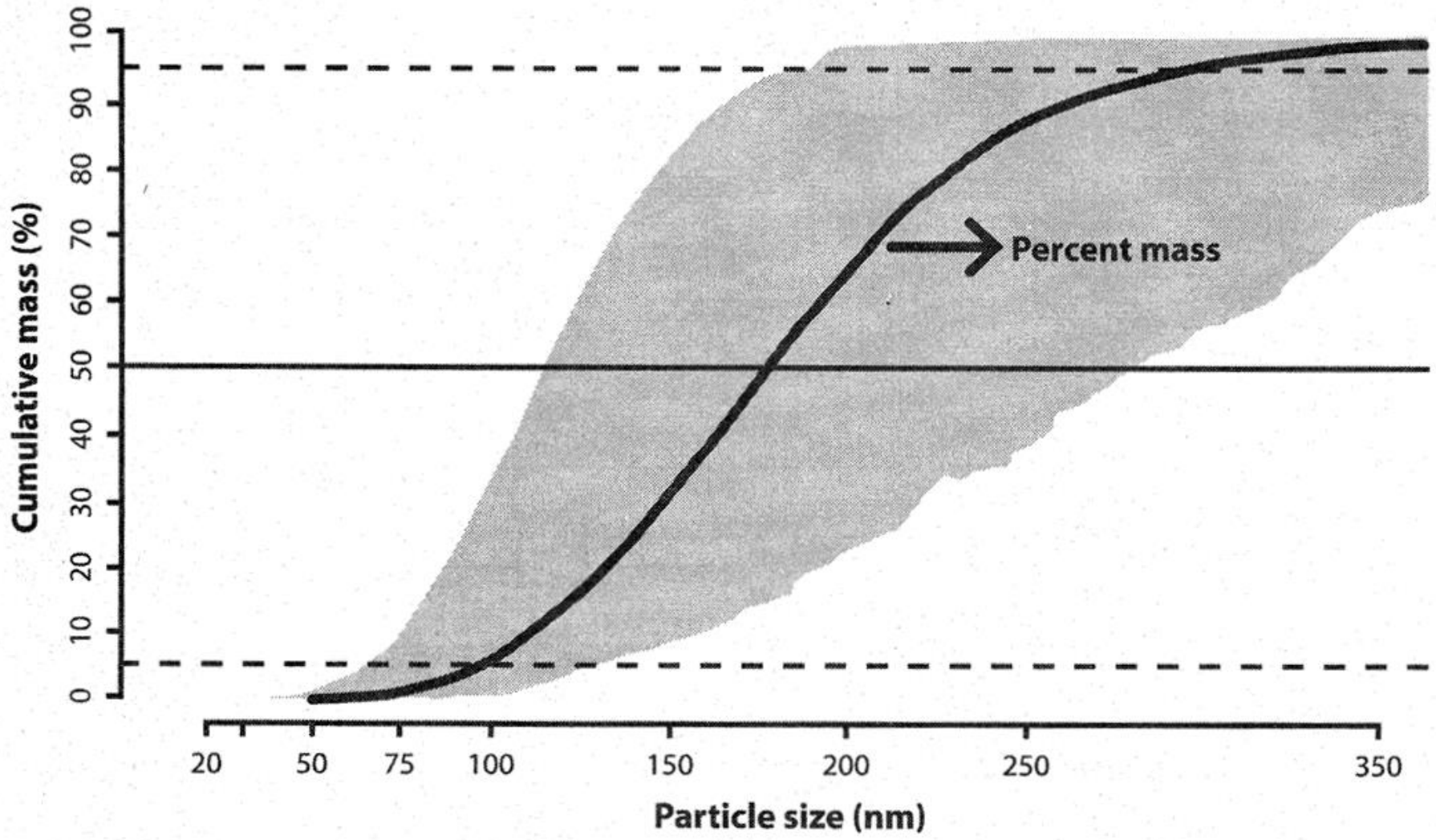
- CCFA agreed the safety of TiO2 as a colouring agent in foods should be re-evaluated by the JECFA. This was based on the safety concerns raised in the EFSA re-evaluation.

2023

- TiO2 reevaluated by JECFA at the 97th meeting.

- The Committee considered that toxicological studies that used E171 (INS 171) as the test substance are representative of the article of commerce.
- Engineered nanoparticle test materials have significantly lower particle size distribution ranges and different physicochemical properties and are not considered to be representative of INS 171.

INS 171 Particle Size Distribution (TEM)



JECFA TiO2 (INS 171)

- Various studies conducted in experimental animals, mainly with INS 171, have demonstrated that the absorption of TiO2 is very low (< 0.00075%)
- In human studies with exposure to TiO2 (up to 300 mg), very limited absorption is seen
- Main studies conducted by NCI (subchronic and chronic exposure to Unitane 0–220 in the diet), no toxic effects noted with NOAELs of 7500 mg/kg bw per day (mice) and 2500 mg/kg bw per day (rat)
- JECFA noted that the available data did not provide convincing evidence of genotoxicity for INS 171, but recognized the limitations of the current methodologies with respect to the testing of poorly soluble particulate materials.
- Negative effects seen with MN and CA assays may be related to very low absorption while positive results may be associated with oxidative stress and/or inflammation (threshold)

- EOGRT study, conducted according to OECD guidelines, showed no effects on reproduction in rats exposed to E171 in the diet at doses up to 1000 mg/kg bw/day.

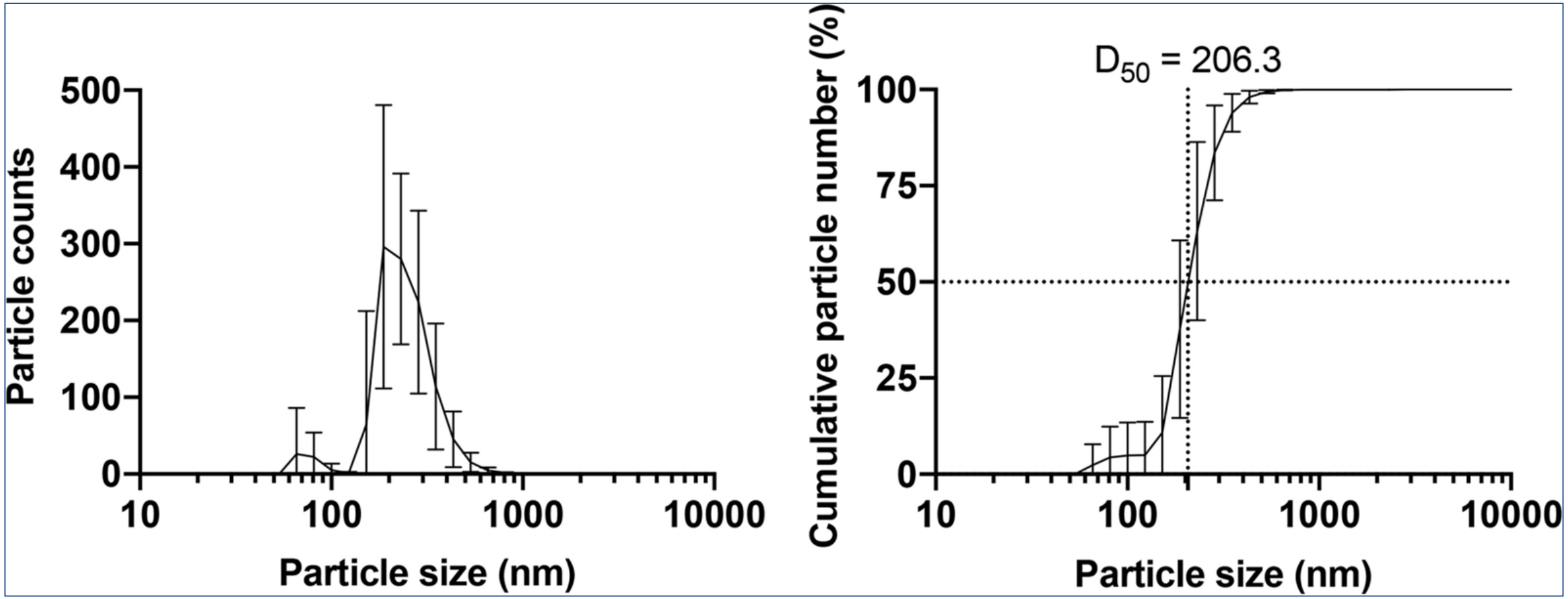
JECFA TiO2 (INS 171)

- Special studies have looked at the ability of TiO2 to promote colon tumours (ACF)
- When E171 was administered in drinking water, ACF ↑
- Similar effects not seen when E171 was administered via the diet at doses up to 236 mg/kg bw/day
- Additional studies with E171 dosing either via drinking-water or by gavage, involving sonification of the test material prior to dosing, have reported GI tract effects (hyperplastic epithelial changes in the colon, gut homeostasis disruption, cytokine markers of colon inflammation) but studies were considered to be of questionable relevance
- A large number of toxicological studies have been conducted using nanoparticles which have size distributions and physicochemical properties not comparable to INS 171. JECFA concluded these studies were not relevant to the safety assessment of INS 171.

JECFA TiO2 (INS 171)

- Certain toxicological effects attributed to TiO2 are mainly associated with method of dosing, particle size distribution and/or different physicochemical properties specific to NPs
- Non-food TiO2 manufacturing methods utilize different precursors, additives and size control agents, which impart specific sizes, narrow size distributions and unique geometries
- The use of E171 as a test material in biological studies should allow the identification of possible hazards from the fraction of particles within food-grade TiO2 that are in the nanoscale range (30-100 nm).
- Considering the very low bioavailability and absence of consistent toxicological effects associated with INS 171, JECFA reaffirmed the ADI “not specified” established in 1969.
- TiO2 (INS 171) food additive specifications revised to describe the manufacturing process which produces a product with a particle size range between 200 and 300 nm.

Particle size distribution of 6 nm TiO2 NPs in solution



Akagi et al., 2023

Summary of Main Studies Conducted with INS 171 (E171)*

1. NCI (1979) - cancer bioassay with Unitane® 0-220; chronic exposure to high doses in feed provided no evidence of toxicity of TiO_2 in rats or mice

- ❑ JECFA considered that the test material is representative of food additive TiO_2 and there was no evidence of carcinogenic effects
- ❑ EFSA concluded that "this study was not appropriate to ascertain the absence of a potential to elicit chronic toxicity and carcinogenicity by TiO_2 nanoparticles"

2. Bettini et al., 2017 - E171 treatment (gavage) produced inflammatory effects in the colon and initiated preneoplastic lesions (aberrant crypt foci (ACF)); also promoted the growth of ACF (DMH initiation) after E171 dosing in drinking water, dispersed in 0.05% BSA and ultrasonicated (Nanogenotox protocol)

- ❑ JECFA considered that additional studies with dietary exposure to E171 (Blevins et al., 2019) and gavage exposure (Han et al., 2020) to non-sonicated E171 produced no histopathological effects in the colon. Relevance of Bettini et al. study to dietary TiO_2 exposure was questioned.
- ❑ EFSA stated that E171 administration by gavage may induce ACF in male rats when the test substance is pre-dispersed and stabilised in a liquid medium preventing agglomeration of NPs; E171 also increased the number of ACF in a colon-tumour model. Considered that exposure to TiO_2 NPs was uncertain in the negative studies investigating ACF formation.

Summary of Main Studies Conducted with INS 171 (E171)*

3. EOGRT (Battersby et al., 2024) – E 171 was administered in feed, doses of 0, 100, 300 or 1000 mg/kg bw/day.

- ❑ No systemic toxicity or reproductive effects, no treatment-related histopathological changes, and no ACF in the colon. No pre-/postnatal developmental changes, including neurotoxicity and no immunological effects.
- ❑ EOGRT – exposure 10 weeks prior to mating until weaning of F1; continued exposure of F1 until weaning of F2 generation.
- ❑ JECFA noted there was a lack of conclusive negative results only for developmental immunotoxicity and considered the NOAEL to be 1000 mg/kg bw/day.
- ❑ EFSA recognized that lack of toxic effects but stated that there are uncertainties regarding the extent to which the particle size distribution of the E 171 used in this study is reflective of the particle size distributions of E 171 when added to foods†


рахмат
danke
謝謝
ngiyabonga
spas
teşekkür ederim
Баярлалаа
mersi
kia ora
barka
welalin
tack
mahalo
tapadh leat
спасибо
faafetai lava
vinaka
спасибі
blagodaram
dank je
misaotra
matondo
paldies
grazzi
thank you
gracias
хвала
kiitos
dankie
nanni
nandri
dhanyavad
mauruuru
köszönöm
akun
dankon
aćiū
asante
manana
obrigada
tenki
bedankt
bayarlalaa
gràçie
hvala
enkosi
djiere dieuf
tau
mochchakkeram
murakoze
дякую
mamnun
chokrane
dziękuję
chnorakaloutioun
gratias ago
gràcies
sulpáy
taiku
go raibh maith agat
sobodi
děkuji
obrigado
sukriya
kop khun krap
sagolun
arigatô
takk
dakujem
trugarez
mèsi
didi madloba
najis tuke
ありがとう
tanemirt
grazie
rahmet
terima kasih
rahmat
kam sah hamnida
diolch
dhanyavadagalu
shukriya
mercé
мерси
شكرًا لك
তোমাকে ধন্যবাদ
감사합니다
xièxie
ευχαριστώ
merci